dose of the drug, the risk of relapse being virtually 100% for those not treated; most experts recommend 5 to 6 mg per kg a day, given once daily five to seven days per week. Both the latter part of the induction phase and the maintenance phase can be given at home. Patients should be monitored fortnightly by an ophthalmologist.

The principal toxic effect of ganciclovir is neutropenia. Dose-limiting neutropenia will develop in about 10% of patients during induction and in 20% during the maintenance phase. We recommend discontinuing therapy if the absolute neutrophil count falls to 500×10^6 per liter. After the granulocyte count returns to baseline, many patients can tolerate a reduced dose. Synergistic toxicity with zidovudine (AZT) is nearly universal, and only a small proportion of patients will be able to tolerate even reduced doses of AZT with maintenance ganciclovir. Other adverse effects, such as thrombocytopenia, hepatitis, eosinophilia, nausea and vomiting, confusion, and rash, are less common and are rarely dose limiting.

As the first drug effective against CMV disease, ganciclovir is a major therapeutic breakthrough, but it is toxic, dose-limiting adverse reactions are common, and it must be given by intravenous infusion. Therapy with this drug should therefore be reserved for patients with sight-threatening CMV retinitis.

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REFERENCES

Jacobson MA, Mills J: Serious cytomegalovirus disease in the acquired immunodeficiency syndrome (AIDS)—Clinical findings, diagnosis, and treatment. Ann Intern Med 1988; 108:585-594

Jacobson MA, O'Donnell JJ, Porteous D, et al: Retinal and gastrointestinal disease due to cytomegalovirus in patients with the acquired immune deficiency syndrome: Prevalence, natural history, and response to ganciclovir therapy. Q J Med 1988; 67:473-486

Mills J, Jacobson MA, O'Donnell JJ, et al: Treatment of cytomegalovirus retinitis in patients with AIDS. Rev Infect Dis 1988; 10 (suppl):S522-S532

Monitoring Sodium Warfarin Therapy Using the International Normalized Ratio

THE PROTHROMBIN TIME (or prothrombin ratio), the time-honored test used to monitor the anticoagulant effect of sodium warfarin therapy, is gradually being supplemented or replaced by a new measure, the international normalized ratio (INR). The use of the INR is being adopted because the thromboplastin reagents used in different laboratories to measure the prothrombin time may have significantly different sensitivities to warfarin-induced changes in vitamin K-dependent clotting factors. The prothrombin time results from two different laboratories on a single specimen of plasma may show a difference in the measurement as great as two to three seconds! Thus, a patient who has an apparently "therapeutic" prothrombin time measurement in one laboratory may have a nontherapeutic prothrombin time result in a different laboratory.

Conceptually, the INR standardizes prothrombin time measurements by taking into account the sensitivity of the thromboplastin reagent being used. Mathematically, the $INR = (PR)^{ISI}$, where the PR is the prothrombin ratio—a patient's prothrombin time divided by the control prothrombin time—and the exponent is the international sensitivity index (ISI) of the reagent. Thus, the INR is identical to the prothrombin ratio when the ISI is 1.0. In Great Britain, where human brain thromboplastins are used, the ISI values are close to 1.0, but in the United States, where rabbit brain thromboplastins are used, ISI values are notably higher, in the range of 1.9 to 2.6.

Recently published guidelines for managing oral anticoagulant therapy define optimal therapeutic target ranges using INR units. Most thromboembolic disorders can be successfully treated using "low-intensity" oral anticoagulation therapy, with the INR between 2.0 and 3.0. These conditions include the treatment of deep vein thrombosis and pulmonary embolism; the prevention of venous thromboembolism in patients undergoing a high-risk surgical procedure; and the prevention of systemic embolization in patients with tissue heart valves, valvular heart disease, atrial fibrillation, and after an acute myocardial infarction. "High-intensity" anticoagulation therapy, with the INR between 3.0 and 4.5, is necessary to prevent systemic embolization in patients who have a mechanical prosthetic heart valve and to treat patients who have a thromboembolic complication while on low-intensity therapy.

If a clinical laboratory does not provide the INR value with each prothrombin time, it is possible to determine it by requesting the ISI value of the thromboplastin reagent and finding the INR value on a published nomogram. (The INR value can also be easily calculated using a pocket calculator equipped with logarithmic and exponential functions.) If the ISI of the thromboplastin reagent is unknown, there is no way to calculate the INR value. Assuming that a thromboplastin reagent has an ISI value of 2.4 and that the control prothrombin time is 12 seconds, the low-intensity INR range of 2.0 to 3.0 is equivalent to a prothrombin time between 16 and 19 seconds, and the high-intensity INR target range of 3.0 to 4.5 is equivalent to a prothrombin time between 19 and 22.5 seconds.

The widespread use of the INR will allow a direct comparison of results from different clinical laboratories, but it will undoubtedly take time for clinicians to become familiar with INR units, particularly the fact that for any change in a patient's coagulation status, the INR will change more than the prothrombin time. For example, if the ISI of a thromboplastin reagent is 2.4, an increase in the prothrombin time from 18 to 24 seconds more than doubles the INR value, which rises from 2.6 to 5.2. Although using the INR will require some adjustment, it is certainly a step in the right direction of achieving better control of anticoagulation therapy.

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REFERENCES

Hirsh J, Levine M: Confusion over the therapeutic range for monitoring anticoagulant therapy in North America. Thromb Haemost 1988; 59:129-132

Hirsh J, Poller L, Deykin D, et al: Optimal therapeutic range for oral anticoagulants. Chest 1989; 95 (suppl):5S-11S

Poller L: A simple nomogram for the derivation of international normalised ratios for the standardisation of prothrombin times. Thromb Haemost 1988; 60:18-20

Turpie AG, Gunstensen J, Hirsh J, et al: Randomised comparison of two intensities of oral anticoagulant therapy after tissue heart valve replacement. Lancet 1988; 1:1242-1245

Medical Treatment of Breast Cancer

THE MANAGEMENT OF carcinoma of the breast has been under intense review for the past decade and has been the source of several well-constructed, multi-institutional clinical trials. As data from these trials have matured, they have changed the practice of cancer management.

Recently eight-year follow-up data have been presented